REMARKS

Cliams 1-3 and 5-23 are pending in the application.

Rejections

(1). Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,089,432 to Crankshaw et al. in view of US 5,549,561 to Hjertman.

The Examiner alleges that Crankshaw discloses the invention substantially as claimed by applicant.

In particular, it is alleged by the Examiner that Crankshaw discloses:

the structure of a vial 11 with two chambers 13, 14 a stopper 17 intermediate the chambers, and an upper stopper 23;

that movement of the upper stopper is an actuating means that pushes the intermediate stopper out of its seal with the constricted portion 16 of the vial, allowing the contents of the two chambers to mix within the combined volume of the two chambers; and

the cap 44 over the top of the stopper, a thin wall of the stopper for needle piercing, and the connections, sleeves, and locks of the claimed vial.

The Examiner acknowledges that Crankshaw fails to disclose that the upper chamber is filled with an aqueous suspension and the lower chamber is filled with a gaseous medium. The Examiner goes on to state that Crankshaw does teach that the purpose of the two-compartment vial is to provide a stable storage solution wherein two substances, which may include a medication, may be stored completely independently from one another, and that such independent storage is used when the combination of the substances in the first and second vials reduces the stability and shelf life of the combined solution or medicine.

Hjertman is cited as disclosing a medicament vial with a first and second chamber 6, 7, separated by barrier 8, and a third chamber 15 filled with a gaseous medium, separated by barrier 13, and that during operation, chambers 6 and 7 are combined, creating a single chamber with an aqueous suspension therein, separated from gaseous chamber 15 by barrier 13 (citing FIG 2, column 5). This arrangement is stated by the Examiner as allowing for the storage of incompatible components in a single vial while providing sufficient headspace in chamber 15 to mix the medicament prior to patient administration.

The Examiner infers from the combined disclosures of Crankshaw and Hjertman that it would have been obvious to one having ordinary skill in the art at the time of invention to provide the vial disclosed by Crankshaw with the aqueous suspension and empty chamber disclosed by Hjertman in order to provide sufficient space for agitation prior to patient administration, as taught by Hjertman.

It is respectfully submitted that Crankshaw only specifically discloses one vial configuration, i.e., that wherein an upper compartment is filled with a powdered medication separated by a moisture barrier from the lower chamber filled with a solvent. While Crankshaw may state that this configuration is a particular utilization of the invention, and further states (at column 5, lines 54-59) that, "[a]lthough a particular preferred embodiment of the invention has been disclosed in detail for illustrative purposes, it will be recognized that variations or modifications of the disclosed apparatus, including the rearrangement of parts, lie within the scope of the present invention", there is **no guidance** in Crankshaw as to other contents of the compartments. Crankshaw does not disclose or suggest a gas impermeable septum separating a compartment containing a formulation of a solid particulate form of a drug substance in an aqueous medium providing controlled flocculation and eliminating the head space in the compartment to prevent oxidation of an ingredient in the formulation from a second compartment comprising a gaseous component.

Hjertman is alleged to overcome the shortcomings of Crankshaw et al. Hjertman is said to disclose a medicament vial with a 1st and 2nd chamber 6, 7, separated by a barrier 8, and a 3rd chamber 15 filled with a gaseous medium, separated by a barrier 13. This disclosure relates to the triple-chamber injection cartridge shown in Fig. 2 of Hjertman. A triple-chamber arrangement clearly can not be combined with the dual-chamber arrangement taught by Crankshaw et al. in any way to be pertinent to the present invention. However, the Examiner suggests that the pertinent situation arises during operation of Hjertman's injection cartridge, when the compartments 6 and 7 are combined to create a single chamber with an aqueous suspension therein, which is separated from gaseous chamber 15 by barrier 13. That is to say, the created single chamber 6+7 would correspond to the 1st chamber of the present invention, and gaseous chamber 15 would correspond to the 2nd chamber of the present invention.

Firstly, it would appear unlikely that one having ordinary skill in the art would try to modify the vial of Crankshaw et al. based on the disclosure of the injection cartridge

of Hjertman **as it appears at the moment of use** to provide a vial with better storage properties – unless, possibly, using hindsight based on an ex-post-facto analysis of the present invention.

Secondly, it is submitted that even if one were to modify the vial of Crankshaw et al in such a way, he would not obtain the claimed invention. The present invention taken as a whole involves the prevention of oxidation of an ingredient in a formulation of a solid particulate form of the drug substance stored in one compartment of a vial as an aqueous medium providing controlled flocculation and eliminating the head space in the compartment separated from a second compartment comprising a gaseous component by a gas impermeable septum, which when breached just prior to administration provides headspace for agitation of the formulation.

Neither Crankshaw et al. nor Hjertman suggest any chamber that is substantially filled with a parenterally deliverable aqueous suspension that comprises an aqueous medium with a drug in solid particulate form suspended together with wetting or suspending agents in an amount effective to provide controlled flocculation of the drug, where at least one ingredient of the formulation is susceptible to oxidative degradation.

Likewise, none of said references suggests any actuating means effective to bring the aqueous suspension and the gaseous medium into contact by breach of the septum such that the gaseous medium acts as an effective headspace for agitation of the formulation. The passage in Hjertman alluded to in the present Office Action, i.e. column 6, lines 20-25 of Hjertman, only says that

> "It goes without saying that the capacities of the rear chamber 7, the front chamber 6 and the space 15 should be adapted to each other in such a way that there will be sufficient room in the front chamber for the solution or dispersion of the solid product 10 and the soluble medium in the liquid product 11 when all the liquid has been transferred from the rear chamber 7 into the front chamber 6, and the front movable wall 13 is in its foremost position."

There is no discussion of any headspace in this passage; it only says that there should be sufficient room in the front chamber for the solution or dispersion of the solid product 10 and the soluble medium in the liquid product 11 when all the liquid has been transferred from the rear chamber 7 into the front chamber 6. Further, the chamber separating septum 13 of Hjertman has a different function than the septum as claimed

with the present invention. The septum 13 of Hjertman is arranged as a movable wall having a foremost position closed to the front of cartridge at which position it can penetrated with a needle or cannula to establish liquid contact with the injectable fluid (c.f. col. 6, lines 25-30). Clearly, this arrangement is never intended to form an effective headspace for agitation over the injectable liquid in chamber 6 of Hjertman.

Also in contrast to the present invention, which comprises the introduction of an effective headspace to actively support re-suspension of settled drug particles for generating a homogenous suspension withdrawable into a syringe for administration, Hjertman teaches the presence of a gas medium that is soluble in the liquid product for the purpose of avoiding air bubbles in the product to be injected. To the skilled artisan, it would be obvious that Hjertman intends to solve a completely different technical problem than the present invention, namely to counteract an unwanted bubble formation when reconstituting freeze-dried proteins for injection. In this context, it is clear that chamber 15 in Fig. 2 of Hjertman does not provide, and was not intended to provide, an effective headspace for agitation.

Therefore, Hjertman actually teaches away from having any headspace in combined rear chamber 7 and front chamber 6, as this would contravene one the major objects of Hjertman's teaching, namely to avoid air bubbles in the preparation to be injected.

For the reasons given above, it is submitted that claims 1-3 are not made obvious by US 4,089,432 to Crankshaw et al. in view of US 5,549,561 to Hjertman. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

(2). Claims 5-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,089,432 to Crankshaw et al in view of US 5,549,561 to Hjertman, further in view of US 6,481,435 to Hochrainer et al.

Crankshaw and Hjertman are discussed above.

Hochrainer is cited as disclosing that steroids are often packaged in two-chambered dispensing vials in suspensions for administration to a patient in various concentrations (citing column 4, lines 5-12, 38-50, columns 5-6).

As previously submitted, Hochrainer et al. does not disclose a two-chamber vial in the meaning of the present invention and can therefore not lead the skilled person towards the invention as claimed, either alone, or together with the combined teachings of Crankshaw and Hjertman. Hochrainer et al. is silent with respect to air as the gaseous medium separated by a gas impermeable barrier form the drug and ingredient

susceptible to oxidative degradation. Hochrainer et al. adds nothing over Crankshaw et al. with respect to the gaseous medium being air.

For the reasons given above, it is submitted that claims 5-23 are not made obvious by US 4,089,432 to Crankshaw et al. in view of US 5,549,561 to Hjertman and US 6,481,435 to Hochrainer et al. No *prima facie* case of obviousness having been made, it is not necessary for Applicant to make a showing of unexpected results.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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